BASIC SCIENCE



The retinal venous pressure at different levels of airway pressure

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Abstract

Purpose To investigate retinal venous pressure (RVP) as a function of airway pressure (AirP) during the Valsalva maneuver (VM) in human subjects.

Methods Forty-three healthy volunteers (age, 22.0 (2.3) years) (median and interquartile range) were investigated using the following instruments: dynamic contour tonometer, contact lens dynamometer (CLD), and aneroid manometer. The following measurements were performed in their left eyes: tonometry and dynamometry during VM at different levels of airway pressure (AirP = 0, 10, 20, 30, and 40 mmHg).

Results The median RVP during spontaneous breathing (AirP = 0) was 19.7 (6.4) (median in mmHg (interquartile range)) and the intraocular pressure (IOP) in mydriasis was 16.3 (3.1) mmHg. Spontaneous pulsation occurred in 58.1% of the subjects. RVP increased nonlinearly. The coefficient of variation of four individual measurements of RVP at each pressure level averaged 8.1 (7.6) %. At different AirP levels of 10, 20, 30, and 40 mmHg, the following RVPs were measured: 29.6 (12.6); 34.2 (12.8); 38.0 (10.5); and 40.3 (11.0), respectively. The rise of RVP (Δ RVP) during VM was significantly higher than that of Δ IOP (p < 0.0001, Wilcoxon test). Δ RVP between 0 and 40 mmHg AirP was 20.6 mmHg and Δ IOP 1.5 mmHg. The steepest slope of the RVP/AirP curve was observed at the first step from 0 to 10 mmHg of AirP (Δ RVP = 9.9 mmHg).

Conclusion A nonlinear relationship between RVP and AirP was found during VM. Small rises in AirP increase the RVP and affect retinal circulation.

Keywords Airway pressure \cdot Retinal venous pressure \cdot Intraocular pressure \cdot Ophthalmodynamometry \cdot Tonometry \cdot Valsalva maneuver

Introduction

During the Valsalva maneuver (VM), the intraocular pressure (IOP) increases due to elevated airway pressure (AirP) [1–3]. This may be explained by an increased pressure in the veins of the head [4], resulting in enhanced filling of the choroid and impairment of the aqueous humor drainage.

Various studies have shown that playing brass and woodwind instruments (implementing VM) causes a temporary elevation in IOP and blood pressure (BP), depending on the tone frequency [5, 6]. In a recent study, it was also shown that retinal venous pressure (RVP) increases during VM [7], but the quantitative dependency of RVP on AirP has not been investigated.

A decisive factor for a sufficient supply of oxygen is the perfusion pressure in the prelaminar layer of the papilla. At this site, the venous outflow encounters a higher resistance as it takes place via the central vein of the retina [8]. As a consequence, significant elevations in RVP may lead to an insufficient blood supply and to damage of the optic nerve.

Contact lens dynamometry (CLD) makes the RVP accessible in a simple manner. In the present study, IOP and RVP were measured at five specified AirP levels to establish a quantitative relationship between these parameters in healthy subjects.

Methods

In the present prospective, cross-sectional study, 43 healthy volunteers were included. After verification of inclusion and exclusion criteria, the subjects were informed about the study and written consent was obtained. The study was approved by

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the Institutional Ethics Committee of the Technical University of Dresden and performed in accordance with the Declaration of Helsinki. Description of the study population is given in Table 1. Inclusion criteria in the study were the following: age 18–40 years, spherical refraction equivalent ≥ -4.9 or \leq 4.9 dpt and an upper arm width of 24–41 cm. Subjects were excluded from the study when having one of the following conditions: intraocular or extraocular inflammation, retinal detachment, corneal scars, blurred optical media, monophthalmia, previous eye surgery, glaucoma and systemic diseases such as peripheral artery occlusive disease, diabetes mellitus, coronary heart disease or myocardial infarction, arterial hypotension or hypertension, sleep apnea syndrome, migraine, stroke or hyperlipidemia. All measurements were done in left eyes.

The examination procedure was performed in the following manner. Measurement of best corrected visual acuity and objective refraction was performed (RF-10 Auto refractometer, Canon). Subsequently, systolic and diastolic blood pressure (BP) in the subclavian artery was determined by the oscillatory cuff method at the upper arm (M5 Professional, Omron, Mannheim Germany). Heart rate was measured manually while sitting. All further investigations were only performed in left eyes under local anesthesia (Proparakain POS® 0.5%, Usapharm, Saarbrücken). Before and after pupil dilation (Mydriatikum Stulln® eye drops, Pharma Stulln GmbH, Stulln), IOP was measured using dynamic contour tonometry (DCT; Ziemer, Port, Switzerland) [9]. In the absence of a spontaneous pulsation in the central retinal vein (SVP) or in one of the branches, RVP was measured using contact lens dynanometry (CLD; Imedos, Jena, Germany) without increasing AirP (AirP = 0 by definition). Four readings were recorded in quick succession. In case an SVP was observed, RVP was set to the value of the initial IOP in mydriasis. Then RVP was measured during enhanced AirP (VM). While sitting at the slit

 Table 1
 Description of the subject parameters: median (interquartile range)

n	43
m/f	33/10
Age (years)	22.0 (2.3)
BP, systolic (mmHg)	120 (10)
BP, diastolic (mmHg)	80 (5)
Body mass index	22.3 (2.5)
IOP, miosis (mmHg)	15.0 (3.2)
IOP, mydriasis (mmHg)	16.3 (3.1)
Spherical equivalent (dpt)	-0.88 (1.44)
SVP present	25
SVP absent	18

BP blood pressure, *IOP* intraocular pressure, *SVP* spontaneous pulsation of the central retinal vein, *dpt* dioptries, *m* male, *f* female

lamp, the subjects closed their lips and forcibly exhaled into an aneroid manometer (Fazzini, Vimodrone, Italy). In total, RVP was measured at 0, 10, 20, 30, and 40 mmHg of AirP. The four levels of elevated AirP were randomly assigned to steps A–D. The subjects started with step A followed by steps B–D. Four CLD readings were taken in quick succession at each step. After each AirP step, a 5-min break was to be taken in which BP and pulse rate were determined.

Immediately prior to AirP steps B, C, and D, IOP was measured, first without increasing AirP, then during elevated AirP of the corresponding AirP step. After the last CLD measurement (AirP step D) BP, heart rate and IOP were measured again during normal breathing.

Statistical analysis

All data were collected in a database (Microsoft Excel 2016) and prepared for statistical analysis by the statistics program SPSS Version 11.5 for Microsoft Windows (SPSS Inc., Chicago, IL, USA) and R version 3.5.3. (R Core Team, 2019). For descriptive analysis, minimum, maximum, mean, median, standard deviation, interquartile range, and absolute and relative frequencies were calculated. Both parametric and nonparametric tests were used to determine statistical significance. With regard to the CLD measurement, a difference of 2.0 mmHg was detected with a significance level of 5%, a standard deviation of 5 mmHg, and a power of 80%. The coefficient of variation and the intraclass correlation coefficient were calculated to determine the measurement repeatability. The frequency of spontaneous or induced vein pulsation was analyzed by chi-square test. Systemic blood pressure values before and after CLD were checked for significant differences using the Wilcoxon test.

To account for the variability of baseline measurements of the participants, the relationship between AirP and RVP was analyzed using a mixed effects model with a random intercept and a fixed effect for AirP. A post hoc pairwise comparison was performed to analyze the RVP values corresponding to the incremental increase in AirP. Statistical analysis was implemented using the R packages lmerTest and emmeans. The p values were adjusted for multiple comparisons using Tukey's method.

Results

The RVP values during elevated AirP showed no significant deviation from the normal distribution. However, the distribution of RVP during normal breathing was right-skewed. For this reason, median and interquartile range was used in the statistics. A spontaneous pulsation occurred in 58.1% of the subjects. RVP at AirP = 0 was 19.7 (6.4) mmHg, and the

intraocular pressure in mydriasis 16.3 (3.1) mmHg. The coefficient of variation of 4 individual measurements of RVP averaged 8.1 (7.6) %. The median pressure increase (ΔP) to cause venous pulsation in subjects without SVP during normal breathing was 8.3 (8.9) mmHg. Table 2 shows the results of RVP and IOP measurements at the following AirP levels: 0, 10, 20, 30, and 40 mmHg.

The increase of RVP and IOP with rising AirP is shown in Fig. 1. There was a nonlinear correlation between RVP and AirP (Fig. 1). The steepest increase of RVP was recorded at Δ AirP = 10 mmHg (Δ RVP = 9.9 mmHg). With each further AirP level, the increase became smaller. The median difference between RVP at AirP = 30 and 40 mmHg was 2.3 mmHg.

The individual RVP curves with increasing AirP as well as the between-subject averages and the corresponding 95% CI are displayed in Fig. 2. Despite a relatively high variability of baseline measurements for different participants, the individual curves show the same increasing trend. The pattern of change in RVP with increasing airway pressure does not vary much between the participants. The results of the mixed effects model with a random intercept and a fixed effect for the AirP confirm that RVP increased 1.5 times (*p* value < 0.0001) from AirP = 0 to AirP = 10 mmHg. With each 10 unit increase in AirP, the RVP values, on average, increased by 20% (*p* value < 10^{-6}).

 Δ RVP between 0 and 40 mmHg AirP was 20.6 mmHg and Δ IOP 1.5 mmHg. During normal breathing, 10% of the subjects had an RVP above 30 mmHg. At AirP = 40 mmHg, 51.2% of the subjects had an RVP exceeding 40 mmHg. There was no correlation with body mass index. The BP did not vary significantly during the course of measurements.

Discussion

In the present study, a nonlinear correlation between RVP and AirP was found. The steepest increase in RVP (Δ RVP =



Fig. 1 Box-and-whisker plot (minimum, maximum, median, and interquartile range): Retinal venous pressure. (RVP, dark patterned boxes) and intraocular pressure (IOP, white boxes) at different levels of airway pressure (AirP = 0 mmHg, 10 mmHg, 20 mmHg, 30 mmHg, and 40 mmHg)

9.9 mmHg) was recorded at a Δ AirP of 10 mmHg. Therefore, small changes in AirP lead to significant elevations of RVP and may influence the perfusion pressure in the retina negatively, especially in the prelaminar layer of the optic nerve head. Inadequate circulation reduces the supply of oxygen and can therefore damage the optic nerve.

The limitation of the increase in RVP during elevated AirP may be due to pressure in the jugular vein in addition to the lower caval vein increases and blood is therefore able to accumulate back into the splanchnic system. The latter is one of the largest blood volume reservoirs in the human body, containing approximately 20% of total blood volume [10]. Due to the high compliance of the splanchnic veins, changes in blood volume are associated with only minor changes in venous transmural pressure [11]. Usually, the effects of increased intrathoracic pressure on venous return are regulated by reflexes

Table 2 Results of contact lensdynamometry and tonometry atdifferent levels of airway pressure(0, 10, 20, 30, 40 mmHg)

AirP (mmHg)	n	RVP (mmHg)				IOP in mydriasis (mmHg)					
		min	Q1	Median	Q3	max	min	Q1	Median	Q3	max
0	43	12.5	15.2	19.7	21.6	40.8	12.3	14.3	16.3	17.4	31.6
10	43	12.3	23.0	29.6	35.6	50.3	12.3	14.2	16.1	17.0	30.0
20	43	16.5	28.1	34.2	40.9	55.4	11.8	14.5	16.6	18.0	29.1
30	43	24.5	32.4	38.0	42.9	56.4	11.5	15.1	16.9	17.8	28.0
40	43	24.4	34.4	40.3	45.4	57.1	11.0	15.8	17.7	19.2	27.6

By definition, respiratory pressure in physiological respiration is zero

n numbers, min minimum, max maximum, Q1 first quartile, Q3 third quartile, RVP retinal venous pressure, AirP airway pressure, IOP intraocular pressure

Fig. 2 Individual retinal vein pressure values (RVP, gray lines), between-subject averages (black thick lines), and corresponding 95% confidence intervals at different levels of airway pressure (AirP = 0 mmHg, 10 mmHg, 20 mmHg, 30 mmHg, and 40 mmHg)



and neurohumoral factors increasing arterial resistance within the splanchnic system [10]. To control hepatosplanchnic blood flow, the venous resistance of the liver decreases, consistent with a passive distention of the venous system [12]. As a consequence, in the splanchnic veins, the stressed volume can increase and thus limit the increase in pressure in the jugular vein. This is comparable with the behavior of the flooding of a polder which prevents an increase in the water level in other areas.

According to Krogh, the fractional distribution of flow between two different areas affects venous return if the vasculature consists of two parallel regions with a different compliance [13]. If the venous resistance is equal in both regions, the time constant of drainage (determined by the product of resistance and compliance) will be longer in the region with the larger compliance. The time constant of drainage of the splanchnic vasculature exceeds the time constant of peripheral vasculature by approximately 20 s [14]. Consequently, a limited regulatory capacity of the veins of the head should be considered for those whose compliance is not adapted to compensate large blood congestion.

Lovasik et al. investigated choroidal blood flow changes during a gradual increase of AirP. They measured real-time changes in the retinal vessel diameter during VM by dynamic vessel analysis [15]. According to Lovasik and Kergoat, the increase in retinal vein diameter is more distinct at high levels of AirP than at lower pressure levels [16]. As a consequence, the venous wall may expand less at lower levels of AirP resulting in an early increase in RVP. The compliance of the central retinal vein may become larger with rising Δ AirP so that at an AirP = 40 mmHg, the increase in RVP equalizes. This is consistent with findings of our study in which a low AirP increase up to 10 mmHg showed the greatest effect on RVP.

In the present study, spontaneous pulsation occurred in 25 of 43 cases (58.1%). In literature, the frequency of SVP in normal subjects is reported to be between 75 and 98% [7,

17, 18]. In contrast to age ranges of 63 to over 69.5 years in previous studies, all subjects in the present study were under the age of 30 years, which may indicate an age-dependency of SVP. Lorentzen observed a slightly increased occurrence of SVP in older age groups [19]. Morgan and coworkers showed a significant dependency (p < 0.0001) between the ophthalmodynamometric force (ODF) necessary to trigger pulsation and age [17]. In older patients, the force required to trigger pulsation was lower. In a follow-up study, this correlation was attributed to the strong correlation between age and pulse pressure (defined as difference between systolic and diastolic blood pressure) since increased pulse pressure values were associated with a lower ODF [20]. An increase in IOP was also associated with increasing age [21]. Thus, in older subjects, IOP values more often exceed venous pressure which may explain an increased incidence of SVP. In another clinical study, SVP occurred more frequently with increasing age, and this was explained by an increase in blood pressure with increasing age [22]. In extrapolation, Stodtmeister et al. reported a significant increase in systemic blood pressure with age demonstrating higher pressures in the ophthalmic artery than in the subclavian artery [23].

With rising AirP up to 40 mmHg, RVP increases much more than IOP. It has been shown by Schmetterer et al. that the thickness of the choroid also rises during VM accompanied by an increase in the volume of the choroid which induces a rise in IOP [24]. However, in the present study, the increase in IOP was relatively small compared with the rise in RVP and may be explained by the anatomical structure of the orbital and choroidal venous system. If the increased pressure in the jugular veins could shoot directly into the choroid via the vortex veins, then the increase in IOP would have to be as high as the rise in RVP. In literature, higher IOP values are reported but after a longer duration of increased AirP [1, 2]. A possible reason could be back pressure due to the filled veins in the orbit. As shown by Reiner and colleagues, the ophthalmic artery releases several branches which are able to gather blood and prevent potential pressure build-up [25]. With regard to the return flow of the blood, veins usually branch similar to arteries. By presuming this analogy, it may be concluded that the central vein of the retina is more directly connected to the cavernous sinus than the ciliary veins. When the pressure in the veins of the head increases, the blood shoots retrograde into the retina rather than into the vortex veins. As venous blood can be distributed backwards in several branches, high pressure cannot build up in the vortex veins.

Another cause for a potential rise in IOP is an elevated pressure in the episcleral veins increasing the resistance of outflow of aqueous humor. However, according to Schuman et al., the impairment of aqueous outflow proceeds even slower than choroidal engorgement [26].

Minor anastomoses between the vortex veins and the anterior ciliary veins draining the choroid and anterior uvea also exist [27–29]. As a consequence, an impaired outflow of venous blood through the vortex veins during small rises of AirP could be compensated for by the anterior vessels [28]. During higher levels of AirP and especially during an increased tonography measurement time (which was not performed in the present study), a congruent IOP rise, as shown in previous studies, may be observed.

Limitations

First, scattering in the measurement values was high at the interindividual level, which may be explained by the diversity of components in the venous system. Further research on these complex mechanisms is certainly needed [10, 30]. Second, due to the low average age and the unequal gender distribution, subjects may not represent the total population. The reason for the skewed distribution of sexes is that CLD measurements were perceived more stressful by females than by male participants. One subject had an increased IOP at AirP = 0 of 31 mmHg in mydriasis, which could indicate a possible undetected ocular pathology and could have led to the abnormal range of IOP for a healthy subject. Despite this outlier, it showed a normal distribution. Third, due to the technical arrangement of the measurements, only left eyes were included. However, as shown by Stodtmeister et al., the results of CLD measurements of the right eyes did not differ significantly from those of left eyes [31]. Fourth, blood pressure was only measured right before tonometry. A continuous measurement of blood pressure during the CLD measurement was not compatible with the experimental design. Fifth, the strain on the eye confined the total level of AirP elevation. However, with regard to brass players, a further increase of AirP exceeding 40 mmHg only occurs in exceptional cases [32]. Sixth, measurement of IOP was performed after increasing AirP for 3-5 s. To observe a corresponding increase in IOP as shown by Aykan or Brody et al., a longer period of measurement would have been necessary [1, 2]. This approach was omitted since

the measurement of RVP at high AirP levels over a long time was considerably more difficult and practically not possible. Seventh, RVP measurements were taken rapidly in a relatively short time. Hence, to minimize influencing factors, the sequence of pressure steps was randomized. Furthermore, the influence of multiple pauses in breathing on the outcome of RVP measurements was not investigated separately because the corneas of the subjects were already stressed by the ongoing procedure. This issue should be investigated in more detail in future studies.

In conclusion, the median RVP rises significantly with even a small increase in AirP and nearly plateaus at an AirP = 40 mmHg. This behavior can be explained by the storage function of the venous system. On the one hand, it may be assumed that the compliance of the retinal vein increases with higher AirPs. On the other hand, a redistribution of blood volume into the splanchnic system may be an explanation for the observed behavior. The large scattering may be caused by the morphological and functional variability of the venous system. The significantly lower increase in IOP at the applied AirP-levels during VM may be explained by a significantly lower pressure in the widely branched veins returning the blood from the choroidea and the episclera.

The Valsalva maneuver may influence perfusion pressure, especially in the prelaminar layer of the optic disc. A frequent exposure to RVP elevations and fluctuations is likely to increase the risk of optic nerve head damage. Regular ophthalmic monitoring for special professional groups such as wind instrument players may therefore be advisable.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The methodology for this study was approved by the ethics committee of Univ. Hospital Carl Gustav Carus, TU Dresden (Ethics approval number: EK 171042017). This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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